Prevention of cardiovascular events in end-stage renal disease: Results of a randomized trial of fosinopril and implications for future studies

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Cardiovascular events (CVEs) are the leading cause of death in chronic hemodialysis patients. Results of trials in non-end-stage renal disease (ESRD) patients cannot be extrapolated to patients with ESRD. It is critical to test cardiovascular therapies in these high-risk patients who are usually excluded from major cardiovascular trials. The study objective was to evaluate the effect of fosinopril on CVEs in patients with ESRD. Eligible patients were randomized to fosinopril 5 mg titrated to 20 mg daily ($n = 196$) or placebo ($n = 201$) plus conventional therapy for 24 months. The primary end point was combined fatal and nonfatal first major CVEs (cardiovascular death, resuscitated death, nonfatal stroke, heart failure, myocardial infarction, or revascularization). No significant benefit for fosinopril was observed in the intent to treat analysis ($n = 397$) after adjusting for independent predictors of CVEs (RR = 0.93, 95% confidence interval (CI) 0.68–1.26, $P = 0.35$). The per protocol secondary supportive analysis ($n = 380$) found a trend towards benefit for fosinopril (adjusted RR = 0.79 (95% CI 0.59–1.1, $P = 0.099$)). In the patients who were hypertensive at baseline, systolic and diastolic blood pressures were significantly decreased in the fosinopril as compared to the placebo group. After adjustment for risk factors, trends were observed suggesting fosinopril may be associated with a lower risk of CVEs. These trends may have become statistically significant had the sample size been larger, and these findings warrant further study.

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End-stage renal disease (ESRD) is increasing in incidence and prevalence around the world. The incidence of ESRD in Europe is reported to range from 92 to 174 per million population among various countries.[1,2] The prevalence in 1999 was 700 per million population.[2] It is estimated that the rate of dialysis is increasing 3–4.3% per year in Europe.[3] Of the European countries that participated in the United States Renal Data System data survey, Germany reported the highest incidence of ESRD, with 174 cases per million population in 2002.[4]

Cardiovascular disease is the primary cause of morbidity and mortality in the ESRD population. It is present in as many as 50–60% of ESRD patients.[4] One-year mortality is approximately 20% among hemodialysis patients, and cardiovascular disease accounts for 45% of this mortality.[4] ESRD is associated with a 2- to 10-fold increased risk of cardiovascular events (CVEs) as compared to patients with normal renal function.[5–8]

Despite the significant degree of morbidity and mortality, limited therapeutic options are available to prevent progression of cardiovascular disease in this growing patient population. The majority of cardiovascular primary and secondary prevention clinical trials have excluded patients with advanced renal insufficiency. Therefore, it is unknown if the results of clinical trials establishing the efficacy of treatment strategies in the management of cardiovascular disease apply to the ESRD population. The German Diabetes and Dialysis study recently showed that lipid-lowering therapy with atorvastatin did not reduce the risk of cardiovascular mortality or morbidity in a hemodialysis

population.[9] These results emphasize the need to study therapeutic agents in the ESRD population, as these patients may respond differently to therapies with proven benefits in non-ESRD patients. The Fosinopril in Dialysis (FOSIDIAL) study was undertaken to evaluate the safety and efficacy of long-term angiotensin-converting enzyme (ACE) inhibition with fosinopril (Fozitec® Merck Lipha, Lyon, France) on cardiovascular clinical outcomes in hemodialysis patients with left ventricular hypertrophy.

RESULTS

A total of 417 patients were recruited for the study in 47 centers. Of these, 397 patients were randomized into the study, 201 to placebo and 196 to fosinopril, and they constitute the intention to treat sample. Fifteen patients (eight placebo and seven fosinopril) withdrew from the study early because of renal transplantation. Protocol violations occurred in two patients (both placebo); thus, the per protocol sample consists of 380 patients. Baseline characteristics between groups were similar, but some differed significantly. Patients in the fosinopril group had a higher baseline risk than patients in the placebo group as reflected by a significantly higher baseline left ventricular (LV) mass index and a trend towards higher rates of diabetes, hyperlipidemia, coronary artery disease, peripheral artery disease, stroke, and prior transplantation. Other significant differences were present including baseline body mass index, duration of renal replacement therapy, and use of oral antidiabetic agents (Table 1). The mean dose of study drug achieved was 13.2 ± 5.5 mg/day in the fosinopril group.

The primary end point event rate was 32.7% over the 2-year follow-up in the whole population. The adjudicated composite annual CVE rate and the individual components are reported in Table 2.

By using Cox proportional hazards survival regression on time to first CVE, a treatment-independent prognostic model was developed in a first step and found that LV mass, age, diabetes, coronary artery disease, stroke, and peripheral artery disease were significant and independent predictors of CVEs. The other available predictors as well as interactions were not significant. In the second step, the treatment variable was entered into this model. No significant adjusted effect of fosinopril was detected (RR = 0.929, 95% confidence interval (CI) 0.68–1.26, $P = 0.35$) (Table 3). The per protocol data were also evaluated as a secondary supportive analysis ($n = 380$). A nonsignificant trend towards treatment benefit for fosinopril was observed (adjusted RR = 0.795 (95% CI 0.59–1.1, $P = 0.099$)) (Table 4).

The mean systolic blood pressure (SBP) at 24 months in the 294 patients with blood pressure data at this time point was 139 ± 22 mm Hg in the fosinopril group and 143 ± 22 mm Hg in the placebo group ($P = 0.07$). Diastolic blood pressure (DBP) was 76 ± 11 and 74 ± 11 mm Hg in the fosinopril and placebo groups, respectively ($P = 0.08$). A summary measure of blood pressure was calculated by averaging the post-baseline blood pressure measurements from 17 visits. A two-way analysis of variance indicated a significant interaction ($P = 0.001$) between treatment and patients who were normotensive (SBP < 140 and DBP < 90) and hypertensive at baseline; thus, the treatment effect was analyzed separately within these patient classifications. No difference was observed between treatment groups for the change in SBP or DBP from baseline to the summary measure for patients who were normotensive at baseline (change in SBP $P = 0.91$; change in DBP $P = 0.981$). A greater reduction in both SBP and DBP was observed for fosinopril-treated patients who were hypertensive at baseline (change in SBP $P = 0.002$; change in DBP $P = 0.01$) (Table 5). The proportion of patients responding to treatment was defined as those with mean SBP < 140 mm Hg and mean DBP < 90 mm Hg, with no hypotensive adverse events. Fosinopril was associated with a greater relative response to treatment compared to placebo in the subset of patients who were hypertensive at baseline (RR 1.85, 95% CI 1.18–2.89, $P = 0.008$) (Table 5) (Figure 1).

Table 1 | Baseline characteristics

	Placebo (*N*=201)	Fosinopril (*N*=196)	*P*-value
Age (years)	67 (8)	67 (8)	0.72
Pre-dialysis BMI	27 (6)	26 (5)	0.02
Baseline SBP (mm Hg)	145 (20)	146 (19)	0.48
Baseline DBP (mm Hg)	77 (11)	77 (11)	0.74
2-week SBP (mm Hg)	148 (21)	147 (22)	0.63
2-week DBP (mm Hg)	78 (12)	77 (12)	0.57
Pulse pressure (mm Hg)	70 (17)	70 (17)	0.79
LV mass index[a]	169 (52)	179 (54)	0.001
Female	99 (49)	90 (46)	0.51
Coronary artery disease history	21 (10)	32 (16)	0.05
Peripheral artery disease history	28 (14)	35 (18)	0.26
Stroke history	11 (6)	18 (9)	0.1
Smoking	22 (11)	24 (12)	0.68
Diabetes	56 (28)	68 (35)	0.12
Dyslipidemia	73 (36)	83 (42)	0.21
Residual diuresis (ml/day)	308 (412)	232 (329)	0.07
Duration of renal replacement therapy (years)	4.4 (4.7)	5.3 (6)	0.04
Duration of dialysis (years)	3.8 (4)	4.4 (5)	0.11
Kt/V	1.3 (0.3)	1.4 (0.5)	0.08
Interdialytic weight change (kg)	2.4 (1)	2.3 (1)	0.22
Study drug treatment duration (days)	541 (269)	537 (271)	0.87
HDL (mmol/l)[b]	1.1 (0.3)	1.1 (0.3)	0.71
LDL (mmol/l)[b]	3.1 (1)	3.1 (1)	0.87
C-reactive protein (mg/l)	13.1 (19.7)	12.5 (17.8)	0.76
Erythropoeitin	156 (78)	157 (80)	0.56
Oral anti-diabetic therapy	3 (2)	12 (6)	<0.001
Insulin	41 (20)	40 (20)	0.99
Lipid-lowering therapy	49 (24)	51 (26)	0.7
Antihypertensive therapy	103 (51)	107 (55)	0.51
Prior transplantation	11 (6)	18 (9)	0.1

BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; *Kt/V*, volume of fluid cleared of urea during a single treatment; LDL, low-density lipoprotein; LV, left ventricular; SBP, systolic blood pressure.
Continuous variables are reported as mean (s.d.), dichotomous variables are reported as *N* (%).
[a]Test performed on log-transformed data.
[b]To convert HDL or LDL from mmol/l (SI units) to mg/dl, divide by 0.0259.

Table 2 | Components of the composite end point (count and 1-year event rate)

	All
Primary end point	130 (16.1%)
All cause death	103 (12.3%)
CV death	63 (7.1%)
Non-CV death	40 (4.9%)
Myocardial infarction	16 (2.0%)
Unstable angina	14 (1.7%)
Coronary revascularization	33 (4.2%)
All cause hospitalization	242 (30.2%)
Heart failure hospitalization	54 (6.5%)
Resuscitated cardiac arrest	5 (0.5%)
Stroke	15 (1.8%)
Mesenteric infarction	5 (0.7%)

CV, cardiovascular.

Table 3 | Cox proportional hazards model: intent to treat sample

Variable	RR	95% CI	*P*-value
Age (years)	1.02	1.00–1.05	0.052
Diabetes	1.34	0.91–1.97	0.136
Coronary artery disease	2.14	1.35–3.39	0.001
Stroke	1.64	0.94–2.87	0.08
Peripheral artery disease	2.00	1.29–3.11	0.002
LV mass[a]	24.05	6.21–93.11	0.000
Fosinopril treatment	0.93	0.68–1.26	0.35

CI, confidence interval; LV, left ventricular.
[a]Log transformed.

Table 4 | Cox proportional hazards model: per protocol sample

Variable	RR	95% CI	*P*-value
Diabetes	1.3	0.87–1.92	0.2
Coronary artery disease	2.44	1.53–3.89	0.000
Stroke	1.68	0.94–2.99	0.08
Peripheral artery disease	2.04	1.30–3.19	0.002
LV mass[a]	18.52	4.62–74.36	0.000
Fosinopril treatment	0.795	0.59–1.1	0.099

CI, confidence interval; LV, left ventricular.
[a]Log transformed.

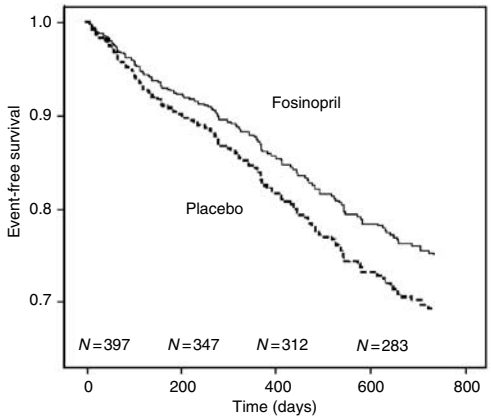

Figure 1 | Occurrence of primary end point by treatment group. Cox proportional hazard survival adjusted for age and baseline severity. ITT analysis: RR = 0.929, $P = 0.35$; per protocol analysis, RR = 0.795, $P = 0.09$. *X*-axis provides time (days) and the corresponding number of at-risk patients.

Safety

After the test dose, six patients experienced symptomatic hypotension and were not randomized in the study. Patients randomized to fosinopril had a higher rate of gastrointestinal side effects (17.5 versus 9.5%). The rates of other adverse events were similar between treatment groups. Baseline potassium was 4.9 ± 0.8 mEq/l in both groups. No significant differences in potassium were observed at any time point during the study. The mean difference between baseline and last visit serum potassium values was 0.1 ± 1.0 and $0.1 \pm .9$ mEq/l in the fosinopril and placebo groups, respectively.

DISCUSSION

Patients randomized to fosinopril appeared to have a lower risk of CVE after adjusting for known risk factors. The unadjusted data are of limited value because of imbalances in important prognostic factors between groups. Thus, the best estimate of fosinopril's effect is provided by the adjusted data. However, definitive conclusions cannot be drawn from this observation. A larger study population is needed to

Table 5 | Change in SBP and DBP

	Placebo	Fosinopril	Difference (95% CI)	*P*-value (ANCOVA)
Normotensive patients (n=159)				
Change in SBP	5.3 (14.2)	5.1 (11.9)	−0.23 (−4.6, 4.1)	0.91
Change in DBP	1.2 (7.4)	1.2 (7.9)	−0.03 (−2.3, 2.2)	0.98
Hypertensive patients (n=238)				
Change in SBP	−5.4 (15.4)	−11.7 (13.4)	−6.3 (−10.3, −2.4)	0.002
Change in DBP	−2.1 (9.1)	−4.9 (9.7)	−2.8 (−5.1, −0.5)	0.01
Response proportion (<140/90 and no DBP value <50 mm Hg)				
Normotensive	65% (84)	71% (75)	RR 1.08 (0.87–1.33)	0.49
Hypertensive	19% (117)	35% (121)	RR 1.85 (1.18–2.89)	0.008

ANCOVA, analysis of covariance; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.

determine if a statistically significant reduction in risk can be detected. Because the overall event rate was lower than anticipated, the FOSIDIAL study lacked statistical power to definitively determine the effect of fosinopril in patients with ESRD and left ventricular hypertrophy.

ACE inhibition is established therapy for prevention of CVEs in patients with prior myocardial infarction (MI), or in other high-risk patients.[10] This guideline recommendation is based on the results of multiple large clinical trials demonstrating a reduction in clinical events for post-MI, heart failure, and stable coronary disease patients receiving ACE-inhibitor therapy.[11–17] However, patients with ESRD on hemodialysis were excluded from these trials. As a result, it is not known if the results of these studies also apply to the large population of ESRD patients at high risk of CVEs. In the Heart Outcomes Prevention Evaluation (HOPE) and Trandolapril in Patients with left Ventricular Dysfunction after Myocardial Infarction (TRACE) trials, patients with serum creatinine above 200 μmol/l (2.3 mg/dl) were excluded.[15,17,18] Serum creatinine above 221 μmol/l (2.5 mg/dl) was an exclusion for participation in the Survival and Ventricular Enlargement study (SAVE).[19] In the recent European Trial on Reduction of Cardiac Events (EUROPA) with Perindopril in Stable Coronary Artery Disease, patients with serum creatinine above 150 μmol/l (1.7 mg/dl) were excluded.[14] The exclusion of patients with renal insufficiency has also been observed in heart failure trials. In an analysis of 59 heart failure randomized controlled trials, renal insufficiency was an exclusion criterion in 11 studies (19%).[20] Thus, the degree to which patients with ESRD may benefit from ACE inhibitor therapy cannot be determined in the absence of a study including this group of patients. A critical need exists to obtain these data as the prevalence of ESRD is expected to climb.[1]

Several lines of evidence suggest that ESRD patients may benefit from ACE-inhibitor therapy to a similar degree as patients without renal failure, although no prospective, randomized clinical trials have been carried out to confirm or refute this hypothesis. A retrospective analysis of the HOPE trial evaluated the relationship between renal function and outcomes by analyzing the effect of ramipril in the subset of patients with renal insufficiency. In this analysis, renal insufficiency was defined as a serum creatinine >124 μmol/l (1.4 mg/dl). A total of 980 patients met this criterion. As expected, cardiovascular and all-cause mortality rates were significantly higher in the patients with renal insufficiency. The risk reduction in the primary end point for ramipril was similar in patients with renal insufficiency (hazard ratio 0.8 (0.59–1.09)) and in those without renal insufficiency (hazard ratio 0.79 (0.7–0.88)). The risk reduction for all-cause mortality appeared to be higher in the renal insufficiency group as compared to those without renal insufficiency (hazard ratio 0.59 (0.42–0.83) versus hazard ratio 0.9 (0.79–1.03), P for heterogeneity $=0.0038$).[18] Importantly, no difference in adverse events was observed between patients with renal insufficiency and normal renal function. However, this subgroup analysis was performed only in patients with mild renal insufficiency, and the results cannot be extrapolated to patients with ESRD on hemodialysis.

A retrospective analysis of the SAVE study also suggested that captopril was equally efficacious in patients with and without chronic kidney disease.[19] The effect on patients with ESRD could not be evaluated in this analysis as patients with serum creatinine above 221 μmol/l (2.5 mg/dl) were excluded from the SAVE trial. Patients were divided into quartiles according to baseline estimated glomerular filtration rate (eGFR). The baseline serum creatinine was 159.1 μmol/l (1.8 mg/dl) and the baseline eGFR was 38 ml/min in the lowest quartile of eGFR. Thus, these data are not reflective of an ESRD population. The retrospective analysis showed that captopril was associated with a greater risk reduction in total mortality and cardiovascular morbidity/mortality in patients with eGFRs of <60 ml/min as compared to those with eGFR above this level. The absolute benefit of captopril was greatest in the lowest eGFR quartiles.[19]

Berger *et al.*[21] conducted a retrospective analysis of the Cooperative Cardiovascular Project to study the patterns of care and effectiveness of post-MI therapies in elderly patients with ESRD. The study sample included patients 65 years of age and older with acute MI. Patient records in the Cooperative Cardiovascular Project database were matched to the United States Renal Data System database to identify those patients with ESRD. The final cohort included 146 765 patients. Of these, 145 740 did not have ESRD and 1025 were receiving chronic hemodialysis. ACE-inhibitor use was lower in patients receiving dialysis who were otherwise candidates for ACE-inhibitor therapy as compared to those without ESRD (27.6 versus. 37.2%, $P<0.001$). Among dialysis patients, ACE-inhibitor use was associated with a significant 30-day mortality reduction (17.3 versus 33.4%, $P<0.001$). After adjusting for baseline demographic and clinical risk factors, the association between ACE inhibitor use and lower mortality persisted (RR 0.58 (0.42–0.77)).[21]

A retrospective analysis reported by Efrati *et al.*[22] also suggested improved survival for hemodialysis patients treated with ACE inhibitors. The investigators studied the effects of ACE inhibitors on mortality in patients undergoing long-term hemodialysis therapy. Patients receiving hemodialysis between 1994 and 2000 were included in the study. Sixty patients had been treated with ACE inhibitors during this period, and 66 patients had not been prescribed ACE inhibitors. Patients who were treated with ACE inhibitors had a significantly lower mortality rate as compared to those who were not treated (RR 0.48, 95% CI 0.25–0.91; $P<0.0019$). Change in blood pressure was not different between groups. These data suggest that a survival benefit may be associated with ACE-inhibitor therapy in hemodialysis patients.[22]

Similar findings have been reported by McCullough *et al.*[23] The investigators analyzed prospectively collected registry data in 386 ESRD patients admitted to a coronary care unit for heart failure or acute coronary syndromes. An

adjusted analysis demonstrated a 37% reduction in all-cause mortality in patients who received ACE-inhibitors versus those who did not during a 3-year follow-up period ($P = 0.0145$). This single-center, retrospective database analysis provides additional data suggesting that ACE inhibitors may be associated with important clinical benefits in patients with ESRD.

Although these retrospective analyses suggest that a clinical benefit is present with ACE inhibitors in ESRD, observational analyses alone are not sufficient to assess the efficacy and safety of ACE-inhibitor use in this setting. The recent study by Wanner *et al.*[9] demonstrates the importance of conducting prospective, randomized trials in this population. Observational data have suggested that patients with ESRD benefit from statin therapy, but this approach had never been tested in a randomized controlled trial. The German Diabetes and Dialysis Study randomized 1225 patients with ESRD to atorvastatin 20 mg/day or placebo. The primary end point of the study was a composite of cardiovascular death, fatal stroke, nonfatal MI, or nonfatal stroke. After 3 years of follow-up, 31.9% of patients in the atorvastatin group and 30.5% of patients in the placebo group experienced the primary end point. No statistical difference was detected between groups. Of concern, there appeared to be a higher risk of fatal stroke in the atorvastatin group as compared to the placebo group (RR 2.03, 95% CI 1.05–3.93, $P = 0.04$). The authors hypothesize that the pathogenesis of CVEs in patients receiving hemodialysis differs from patients without ESRD, and that statin therapy may not influence these pathologic processes. In addition, the authors hypothesized that once patients have progressed to the point of ESRD, they have a lower chance of benefiting from cardiovascular prevention strategies.

Safety is an important concern with the use of ACE inhibitors in this patient population. Patients on hemodialysis receiving either ACE inhibitors or angiotensin receptor blockers have a significantly higher risk of developing hyperkalemia compared with ESRD patients not receiving these drugs, even after adjusting for other risk factors.[24] Importantly, the change in serum potassium observed in FOSIDIAL was minimal, and there was no difference in the rate of hyperkalemia between the fosinopril and placebo groups. Fosinopril had a favorable safety profile in this study that may be related to the unique pharmacokinetic profile of this agent among other ACE inhibitors. It is hepatically and renally eliminated. In the setting of renal failure, it accumulates to a lesser degree than lisinopril or enalapril.[25–27]

Important knowledge has been gained from the FOSIDIAL trial. First, this trial allowed for a contemporary, accurate estimate of overall and CVE rates in patients with ESRD in a typical European country. To adequately test the effect of fosinopril in patients with ESRD in a randomized, placebo-controlled trial, 476 patients per group or almost 1000 total patients would be needed for 90% power to detect a 33% reduction in the event rate, assuming an overall event rate of 32.7%. CVE rates in the ESRD population may differ across geographic regions. These differences should be considered in the design of future intervention studies. Second, a Critical Events Committee used a rigorous adjudication process to classify clinical events. As a result, detailed information was collected on the type of events occurring in this population. These data have not been previously available, and they will guide the development of future studies in this population. It is critical to precisely estimate the event rate for individual components of composite end points, because they are most likely to be used in future trials for the sake of optimizing sample size.

After adjustment for baseline differences and other risk factors, trends were observed suggesting fosinopril may be associated with a lower risk of CVE. These trends may have become statistically significant had the sample size been adequate, and these findings warrant further study in larger trials. The data indicate with 90% confidence that fosinopril was associated with a modest expected CVE risk reduction of at least 0.8–0.9. Further research in an adequately powered study is needed based on these trends and other published data from retrospective and observational analyses. ACE inhibitors are currently used clinically in patients with ESRD, and it is appropriate to study their efficacy and safety in these patients, who are traditionally excluded from cardiovascular clinical trials.

MATERIALS AND METHODS

The design of FOSIDIAL has been published.[28] Briefly, the study was a phase III, controlled, randomized, double-blind study of fosinopril or placebo. Patients were eligible for enrollment if they met the following criteria: men or postmenopausal women 50–80 years of age; hemodialysis for at least 6 months with three sessions per week; and left ventricular hypertrophy defined by a cardiac mass index $>130\,g/m^2$ for men and $100\,g/m^2$ for women within 3 months of enrollment. The major exclusions to participation were ACE-inhibitor use; hyperkalemia ($\geqslant 6$ mmol/l); or hypersensitivity to ACE inhibitors. The study was conducted at 47 centers in France, and it was approved by the local ethics committee on human research. All study procedures were performed in accordance with the Declaration of Helsinki Principles. All patients provided written informed consent.

All patients underwent a 2-week single-blind run-in period. Patients received a test dose of fosinopril 5 mg. Blood pressure was measured every 30 min for 4–6 h after administration of this dose. Patients with symptomatic hypotension or SBP below 95 mm Hg were dropped from the study. Patients were then randomized to receive double-blind treatment with fosinopril or placebo for 24 months. Patients who tolerated the initial dose were entered into a 3- to 6-week up-titration period. The study medication dose was increased weekly in increments of 5 mg until the target dose of 20 mg daily was achieved. Concomitant therapy was allowed during the study period with the exception of ACE inhibitors or angiotensin receptor blockers. The duration of follow-up was 2 years.

The primary end point was the occurrence of CVE, defined as the composite of cardiovascular death, nonfatal MI, unstable angina, stroke, revascularization (percutaneous coronary intervention or coronary artery bypass grafting), hospitalization for heart failure, and resuscitated cardiac arrest at 24 months. Secondary end points

included change in SBP and DBP, individual components of the composite end point, event-free survival, time to first event, all-cause mortality, and all-cause hospitalizations. All clinical events were adjudicated by a Critical Events committee according to pre-established definitions. MI was defined by the presence of at least two of the following criteria: prolonged (>20 min) chest pain, new Q wave (>0.04 s $+>0.2$ mV) in at least two concordant electrocardiogram derivations, new R wave predominant in V1, or CK or CKMB, troponin, or myoglobin greater than twice the upper limit of the normal range. Unstable angina was defined by a prolonged (>20 min) chest pain and ST or T wave electrocardiogram ischemic changes. Heart failure was defined by a period of >24 h hospitalization for new onset or worsening of dyspnea with signs and symptoms of clinical and/or radiological signs of peripheral and/or pulmonary congestion and documented worsening of cardiac function (increase in X-ray cardiothoracic ratio or increase of echocardiogram LV dimension with decrease in LV shortening fraction or increase in heart catheterization pulmonary capillary wedge pressure or LV filling pressure). In addition or alternatively, the dialysis strategy had to be changed for up to one consecutive month, including increase in weekly dialysis duration $>20\%$ and/or increase in baseline weight >1 kg, and/or switch to hemofiltration. These changes could not be in response to an omission or reduction in routine dialysis. Stroke was defined as focal neurological deficit lasting >24 h with concordant documented new computed tomography scan or magnetic resonance imaging cerebral lesion or hemorrhage (excluding iatrogenic or traumatic causes).

Statistical methods

It was originally estimated that 198 patients per group would provide 90% power to detect a CVE relative risk for fosinopril versus placebo of less than 0.66 (true difference of 16%). This estimation was based on an alpha level of 0.05, and an assumed putative placebo event rate of 50% during a 2-year follow-up period. The main analysis was carried out on both an intention to treat basis and on the per protocol sample. The per protocol findings are considered as supportive.

A blind interim analysis revealed an estimated CVE of 30%, a value that was much lower than the anticipated rate of 50%. The hypothesized risk reduction was unchanged, and the corresponding true difference of 10% instead of 16% resulted in a noticeably poor type 2 risk ($\beta = 0.45$). To increase the study's power, an adjustment model was developed to account for differences in clinically relevant predictors. The following factors were included in the model: previous cardiovascular history (stroke, coronary artery disease, peripheral artery disease) and known comorbidities (age, LV mass, diabetes). Center was used as a random variable and was considered to account for possible extraneous variation. A two-stage analysis was planned *a priori*. The first step consisted of detecting determinant predictors using a systematic exploratory stepwise Cox proportional hazards survival regression (including first-order interactions) without entering the treatment effect into the model. Predictors were retained if they were significant at a minimum level ($P<0.15$). In the second step, the treatment effect was tested at a one-sided 0.05 level, after adjusting for the retained predictors identified in the final model found in step 1. Thus, treatment factor and its interactions were adjusted by the retained predictors. This procedure has been shown to be safely used in preserving global type 1 error, and it is recommended in clinical trials where the predictors in a pathology are *a priori* not known.[29]

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